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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,648	04/11/2001	Cy A. Stein	0575/55669-Z/JPW/BJA	2605

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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	7

DATE MAILED: 01/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/832,648	Applicant(s) STEIN, CY A.	
	Examiner Janet Epps	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,26-30 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,26-30 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Inventorship

1. The request to correct the inventorship of this nonprovisional application under 37 CFR 1.48(a) is deficient because:

> The statement of facts by an inventor or inventors to be added or deleted does not explicitly state that the inventorship error occurred without deceptive intent on his or her part or cannot be construed to so state.
>
> It lacks the written consent of any assignee of one of the originally named inventors.

The REMARKS (page 4) section of the preliminary amendment filed 4-11-01, sets forth Robert Rando, and Joshua Ojwang as being co-inventors of the subject matter of claims 26-30. However, Applicant's remarks are uncertain since these claims have not been cancelled, and neither Rando nor Ojwang appear as co-inventors on the Declaration submitted for this application.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 9, 26-30 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pollman et al. and Gibbons et al. (US Patent No. 5,776,905) in view of Manoharan et al. (WO 93/07883 A1).

Claims 9 and 36 are drawn to a composition comprising an antisense oligonucleotide comprising consecutive nucleotides, the nucleotide sequence of which is set forth in one of SEQ ID NOS: 1-13. Claims 26-30 are drawn to a method of promoting the regression of vascular lesions comprising introducing antisense oligonucleotides shown to be effective in reducing bcl-x_L expression into a vascular cell.

Pollman teach inhibition of neo-intimal cell bcl-x expression comprising transfecting a composition comprising Lipofectamine and an antisense oligonucleotide directed against bcl-x into atheromatous (i.e. vascular) lesions in the rabbit carotid artery (Methods section, p. 226). Specific down regulation of the bcl-x_L splice isoform resulted in regression of atheromatous lesions (see Figure 8, page 226). Additionally, Pollman et al. discloses 3 phosphorothioate modified antisense oligonucleotides, wherein antisense sequence-3 (#3; see Methods section, page 226) comprises the consecutive nucleotide sequence of SEQ ID NO: 2 of the instant application. Additionally, Gibbons et al. teach a method for reducing the dimensions of a neointimal vascular lesion in a patient comprising localized delivery of an antisense oligonucleotide that inhibits the expression of bcl-x_L (col.2 lines 28-42). Gibbons et al. teach administration of antisense oligonucleotides comprising methods known in the art for enhancing

the uptake if nucleic acids by cells, for example delivery systems include Sendai virus-liposomes, cationic liposomes polymeric gels or matrices, and porous ballon catheters (col. 7, lines 45-60). Additionally, Gibbons et al. teach that the antisense oligonucleotides used in the method for reducing the expression of bcl-x_L in cells may comprise modifications to enhance oligonucleotide intracellular stability and binding affinity. In a specific embodiment Gibbons et al. teach that the 2'-OH ribose sugar may be altered to form 2'-O-methyl (col. 5, lines 6-28). [It is noted that since the specification as filed does not clearly define what the term "-OMe" is intended to encompass, this term is interpreted as encompassing either "2'-O-methyl" or "2'-O-methoxy."]

Furthermore, neither Pollman et al. nor Gibbons et al. teach the administration of antisense oligonucleotides into cells comprising the use of porphyrin as a delivery agent.

Manoharan et al. teach the design and use of derivatized antisense oligonucleotides, wherein derivatization of said antisense oligonucleotides results in improved transfer across cellular membranes (page 5, lines 7-9). The compounds of Manoharan et al. comprise a plurality of linked nucleosides wherein at least one of the nucleosides is functionalized at the 2'-position with a substituent such as for example, a steroid molecule, a lipid soluble vitamin, a lipophilic molecule and a porphyrin (page 5, lines 20-30).

It would have been obvious to one of ordinary skill in the art, at the time of filing, to modify the teachings of Pollman et al. and Gibbons et al. with the teachings of Manoharan et al. in the design of a method comprising the use of a porphyrin compound in the delivery of antisense oligonucleotides targeting bcl-x_L to vascular lesions. One of ordinary skill in the art would have been motivated to modify the method of delivering antisense oligonucleotides as

disclosed by Pollman et al. and Gibbons et al. by the use of a porphyrin compound since the antisense oligonucleotides of Pollman et al. and Gibbons et al. are intended for delivery into cells, and the modifications taught by Manoharan et al. are disclosed as being useful to confer enhanced cellular uptake to the derivatized oligonucleotide compound. Furthermore, it would have been therapeutically advantageous to modify the method disclosed by Pollman et al. and Gibbons et al. by adding a modification that would increase the intracellular availability of the antisense compounds within the tissues to which the compound is administered.

Therefore, the invention as a whole is *prima facie* over Pollman et al. and Gibbons et al. in view of Manoharan et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 8:30AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps
Examiner
Art Unit 1635

JLE
January 22, 2002